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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
1633	4

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/132,521	Applicant(s) Nagai et al.
	Examiner Stroup, Carrie	Group Art Unit 1633

X Responsive to communication(s) filed on *Feb 11, 1999*.

This action is **FINAL**.

Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

X Claim(s) *1-15* is/are pending in the application.

Of the above, claim(s) *13* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

X Claim(s) *1-12, 14, and 15* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

X Information Disclosure Statement(s), PTO-1449, Paper No(s). *4*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- *SEE OFFICE ACTION ON THE FOLLOWING PAGES* ---

DETAILED ACTION

Applicants' Response to the Office Action, Paper 8 (8/16/99) has been entered. Claim 13 has been canceled. Claims 2-5, 7-12, amended claims 1 and 6, and newly added claims 14 and 15 are currently pending.

Claim Rejections - 35 USC § 112

1. Claims 9 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants' claimed invention is to a method of treating HIV infection in humans via administration of a recombinant Sendai virus vector expressing CXC-chemokine or CC-chemokine (claim 9). Applicants' claimed invention reads on *in vivo* gene therapy, which at the time of the invention and to the present is a highly unpredictable art. Applicants assert in Paper 8, page 3, paragraph 2, that the specification provides teachings on page 8, line 13-page 9, line 6 which are sufficient for one of skill in the field of the invention to make and use without undue experimentation. Applicants also state that the Examiner has pointed to no information that would be needed to practice the claimed invention that would require undue experimentation to determine (Paper 8, page 4, paragraph 1).

On page 9, paragraph 1, the specification teaches that "The dose of the virus vector varies depending on the age, weight, and symptoms of the patients, the administration route, and the kinds of chemokines. The virus vector is administered at .1 to 10,000 virions/cell, preferably .5 to 50 virions/cell." The specification also provides exemplifications wherein pSeVSDF-1α was transfected to v-TF7-3 infected LLCMK2 cells which were subsequently injected into embryonated chicken eggs to amplify the recovered virus, which was then confirmed by SDS-Page,

Northern blot, and Western blot, purified via centrifugation. Anti-HIV activity was also demonstrated via incubating MT4 or PHA-stimulated PBMC cells with the purified chemokines then exposing said cells to tissue culture containing HIV-1 (Examples 1& 2, pg 10). As previously stated in Paper 5, pg 2-3, the specification fails to disclose the appropriate dose per route of administration, methods of effective targeted delivery of a Sendai virus to any specific cell type, such as CD4 T-cells residing in lymph nodes and brain tissue, and methods of producing a high, stable level of chemokine gene expression. Said teachings are not disclosed by the Applicants in the cited reference (Paper 8, page 3, paragraph 2), but are essential for providing *in vivo* gene therapy which would produce stromal derived factor, or any chemokine, at a dose and duration to provide any therapeutic effect to a patient.

As previously stated in Paper 5, page 3, in vivo gene therapy is a highly unpredictable art because there are barriers to the *in vivo* delivery of DNA, the extent of which directly affects the bioavailability and hence the required dose and the level and duration of gene expression to effectively produce a therapeutic protein. These barriers include: (i) the rapid degradation of DNA within tissues or blood by nuclease; (ii) the limited dispersion of DNA from the site of interstitial administration; (iii) the inability of DNA to cross intact basement membranes of the endothelium or epithelium effectively; (iv) the rapid clearance of DNA from the vascular compartment by cells of the reticuloendothelial system; (v) the need for effective interaction with the surface of the target cell to induce internalization; (vi) destruction of DNA in the endosomal/lysosomal compartments by nuclease, acid and/or reducing agents; and (vii) the need to penetrate to the nucleus of cells across the periplasmic membrane and nuclear membrane. Therefore, it is maintained that in light of the absence of teachings within the specification to overcome the unpredictability in the art, such as the specific dose per route of administration, methods of targeted vector delivery to HIV infected tissue, and the appropriate vector construct with promoter and enhancer to ensure a high and stable level of in vivo chemokine gene expression per target tissue type, one of skill in the art would be required to practice undue experimentation to inhibit

the infection of human cells and tissue by HIV via the in vivo delivery of recombinant Sendai viral vectors expressing a chemokine, such as SDF.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1-8, 11-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hasan et al (1997) or Yu et al (1997) in view of Bleul et al (1996) and Calain et al (1993).

Applicants' claimed invention is to a Sendai virus expressing a chemokine, such as CXC stromal cell-derived factor alpha or beta, wherein the vector is disseminative or is infectious and replicates autonomously, but is not disseminative (claims 1-5); a method of producing a chemokine via inserting at least one chemokine gene into a Sendai virus vector, and recovering said chemokine via centrifugation (claims 6-8); and a pharmaceutical composition comprising a recombinant Sendai virus vector expressing stromal cell-derived factor alpha or beta, wherein said vector is disseminative or non disseminative (claims 11 and 12).

Applicants assert that it would not have been obvious to one of ordinary skill in the art to use Sendai virus vector to produce chemokines efficiently and in substantial amounts which can simply and economically be purified by heparin column chromatography. It is noted that the pending claims are not limited to purification by heparin column chromatography or to production of a specific amount of chemokine. Applicants also state that the teachings of Bleul et al, for the administration of SDF-1 for anti-HIV activity is not central to the claimed invention. Applicants method of purification via centrifugation and heparin column chromatography are standard in the art of protein recovery from cells

transfected with a vector (see Yu et al and Hasan et al). Additionally, Yu et al teach that recombinant Sendai virus can be used to produce large quantities of encoded protein, as demonstrated by their recovery of 2.2/microg per 10^6 infected cells, purified with a recovery rate of about 60% for V(+) version, and 6.0microg per 10^6 infected cells for the V(-) version. Therefore it is maintained that the claimed invention is obvious over Hasan et al (1997) or Yu et al (1997) in view of Bleul et al (1996) and Calain et al (1993) to use a recombinant Sendai viral vector to express any chemokine, such as SDF alpha or beta, for the purpose of inhibiting HIV proliferation.

4. Claim 10 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Hasan et al (1997) in view of Bleul et al (1996) and Hasegawa et al (1997).

Applicants' claimed invention is to an *ex vivo* method of gene therapy utilizing recombinant Sendai virus expressing a CXC chemokine for the treatment of HIV infection.

Applicant states that " it would not have been obvious that the recombinant chemokines produced by the method of the present invention could be functionally authentic and could inhibit HIV replication" because one of skill in the art could not have expected the efficient production of recombinant chemokines with a Sendai virus vector (Paper 8, page 6). The Office does not agree. As stated in Paper 8, page 6, Hasan et al teach the use of recombinant Sendai virus for efficacious, high level expression of a firefly luciferase gene, wherein the gene is inserted in the same Sendai N gene and upstream of the ORF region, which is the same site and manner of gene insertion as disclosed by the Applicants with the claimed invention (e.g., specification, pg 9, para 4). Hasegawa et al teaches the use of recombinant Sendai virus for gene therapy, and Bleul teaches the use of SDF to inhibit HIV. Therefore, in light of Hasegawa, Bleul, and Hasan et al it is maintained that the claimed invention was obvious because one of ordinary skill in the art would have expected that recombinant Sendai virus utilized in ex vivo gene therapy could produce

numerous transgenes which were functionally authentic and at a high enough level to provide a therapeutic benefit, such as the use of SDF to inhibit HIV proliferation.

Conclusion

5. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Carrie Stroup

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PRIMARY EXAMINER
GROUP 1800